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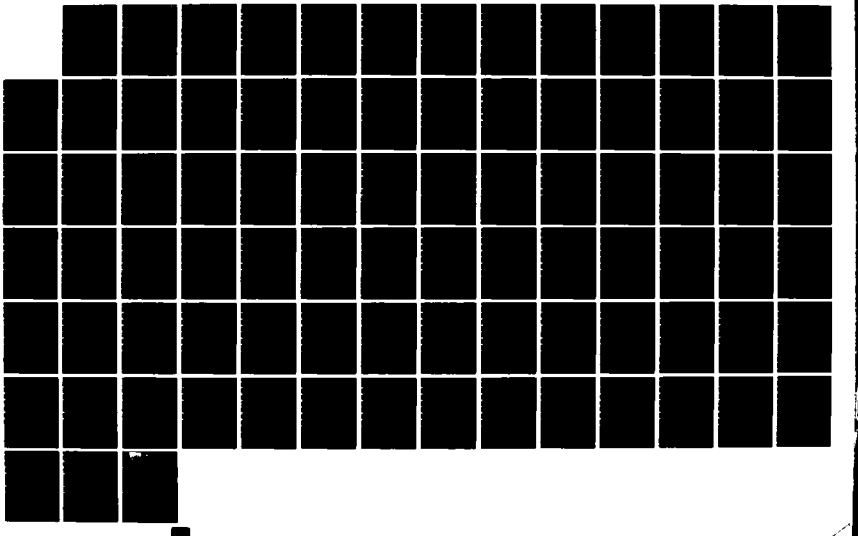

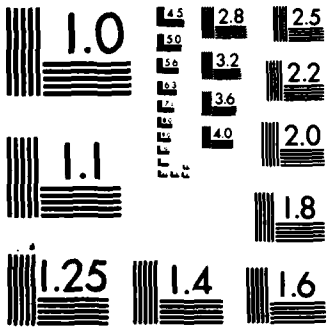

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brain metabolism, shock, infrared spectrophotometry

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

This final report contains detailed documentation of research in the following areas:

1. Intravenous infusion of ATP-MgCl as part of resuscitation from hemorrhagic shock gives transiently better high-energy phosphate levels in the liver with no apparent benefit to the brain.

2. Investigations into combinations of hemorrhagic shock and hypoxia in...

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conjunction with hypothermia show that hypothermia is beneficial during the period of hypoxic hypotension, but continued hypothermia after resuscitation serves no useful purpose.

3. High-frequency ventilation as administered using the principle of oscillation of an insufflated air stream into the trachea provides equal oxygenation at lower airway pressures when compared to jet ventilation and conventional respirator ventilation.

4. Brain high-energy phosphate levels appear to be improved after hypoxic hypotension when resuscitation includes nifedipine. This is most likely due to the vasodilation effect of nifedipine as opposed to an intraneuronal mechanism.

5. Perfluorochemical Fluosol-43 functions adequately as a volume expander and oxygen transport medium when utilized to resuscitate animals from hypoxic hypotension.

6. Exchange transfusions of pregnant ewes utilizing either balanced salt solution or Fluosol demonstrate a clear-cut superiority of Fluosol in terms of the fetal oxygenation as assessed by infrared spectrophotometry.

7. Good correlations between brain metabolism as assessed by near infrared spectrophotometry and direct measurements of intracranial pressure were obtained in a series of cats in whom the intracranial pressure was artificially increased by intracranial instillation of saline. The preliminary indications are that near infrared spectrophotometry may be a useful monitoring device in instances of increased intracranial pressure.

BRAIN METABOLISM DURING INCREASED INTRACRANIAL PRESSURE AS ASSESSED BY NIROSCOPY

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ABSTRACT

Intracranial pressure was increased in cats by infusion of "mock" CSF into the cisterna magna. This condition was then treated by hyperventilation. In addition to direct measurement of intracranial pressure, cerebral metabolism was assessed by near infrared spectrophotometric (niroscopic) measurement of cytochrome $\underline{a},\underline{a}_3$ redox state, and the quantity of reduced (Hb) and oxygenated (HbO_2) hemoglobin in the illuminated brain. Cerebral perfusion was assessed by injection of cardiogreen. Increased intracranial pressure resulted in the expected reduction in cytochrome $\underline{a},\underline{a}_3$, a decrease in HbO_2, an increase in Hb, and a reduction of blood flow. The vasoconstriction produced by hyperventilation, while reducing intracranial pressure, produced a further reduction in cytochrome $\underline{a},\underline{a}_3$ and HbO_2, with no improvement in blood flow. The data illustrate the fallacy of governing therapy solely by intracranial pressure, and demonstrate the need for a direct assessment of brain metabolism. The data also demonstrate the strengths and weaknesses of niroscopy as a non-invasive monitor of the brain metabolism if applied to patients at risk for increased intracranial pressure.

INTRODUCTION

Miller et al[6] noted that when the initial intracranial pressure was greater than 40 mm Hg in head injured patients with mass lesions, the eventual neurological outcome was poor. They further noted that in patients without mass lesions presenting initially with a normal intracranial pressure, a subsequent rise greater than 20 mm Hg was associated with increased morbidity. These observations illustrate that, at the present time, the widespread practice of monitoring intracranial pressure serves two functions, that of providing a prognostic index for future outcome, and as a means of continuously monitoring the progress of a hospitalized patient, allowing rapid intervention at times of increasing intracranial pressure.

The multiplicity of devices for the monitoring of intracranial pressure[5] serves as testimony to the lack of satisfaction with any one method. All currently employed methods are invasive with approximately a 7% incidence of hemorrhage, ventriculitis, meningitis, or infection associated with their use[7]. Furthermore, a measurement of intracranial pressure does not directly measure the blood flow and the metabolic state of the brain.

Because of these perceived shortcomings, we have recently completed a preliminary investigation in which *in vivo* near infrared spectrophotometric (niroscopic) monitoring of brain cytochrome a,a_3 redox state and the quantity of intracranial oxidized and reduced hemoglobin was performed in cats in whom the intracranial pressure had been experimentally increased[1,2], thereby allowing a direct simultaneous assessment of mitochondrial metabolism and intracranial pressure. The optically obtained data correlated well with simultaneously performed direct measurements of intracranial pressure, and had the added potential of being capable of non-invasive acquisition. In

the study reported herein, we have extended these observations by experimentally increasing the intracranial pressure, then reducing intracranial pressure by hyperventilation while simultaneously assessing the metabolic state of the brain using niroscopy. Our hypothesis was that even though reduction of ICP by hyperventilation may lead to improved cerebral perfusion pressure (CPP) the mechanism would be based upon vasoconstriction, reduced blood flow and blood volume and an actual decrement in metabolic support of the tissue, i.e., CPP may improve but at the expense of further tissue hypoxia.

MATERIALS AND METHODS

Ten female cats, 2-3 Kg, were anesthetized with pentobarbital sodium, 35 mg/Kg, injected intraperitoneally. A femoral artery and vein cutdown were performed to allow the injection of drugs, the monitoring of arterial pressure, and the withdrawal of arterial blood for pO_2, pCO_2 and pH determination. A lightly anesthetized state was maintained by intermittent administration of pentobarbital sodium intravenously. A tracheostomy was performed, the animals paralyzed (tubocurarine, 2 mg/Kg, IV) and connected to a Harvard ventilator. The cats were ventilated with room air and the ventilator adjusted to achieve an arterial pCO_2 30-35 mm Hg, pH 7.30 - 7.35, and an arterial pO_2 of at least 100 mm Hg. The cats' heads were then mounted in a stereotaxic holder and a sagittal incision made through the scalp to allow reflexion of the extracranial muscles exposing the skull. The fiberoptic bundle used to deliver light in the near infrared range (see below) was positioned against the parieto-occipital skull on one side and the photomultiplier detector positioned (through a burr hole) over the opposite parieto-occipital region. Dental compound was utilized to insure a rigid, water tight seal around the photomultiplier tube even though the tube was extradural.

The principles of niroscopy have been explained before[8,9]. Briefly, light at 813 nm, an absorption band of oxidized cytochrome $\underline{a},\underline{a}_3$, is utilized to detect the quantity of oxidized cytochrome $\underline{a},\underline{a}_3$ in the illuminated field. Since the spectra of reduced and oxidized hemoglobin overlap that of cytochrome $\underline{a},\underline{a}_3$, additional reference wavelengths of 770 and 905 nm are used and by appropriate algorithms the artifactual contribution of hemoglobin to the cytochrome signal is subtracted out. At the same time, these signals provide information regarding the quantity of reduced and oxidized hemoglobin. Summation of the two hemoglobin signals results in the total hemoglobin which, by inference, represents the total intracranial blood volume in the illuminated field. Cardiogreen dye has an absorption peak at 800 nm. Injection of .007 mg/Kg i.v. through a central venous catheter allows the measurement of blood flow in the illuminated field by integration under the resulting curve using the method of Hamilton[3].

Several modifications in animal preparation were necessary in the cat which we have not employed in previous studies with rats[8,9]. First, it was necessary to reflect the extracranial musculature to avoid unwanted contribution from these tissues. Second, the much greater thickness of the skull of the cat versus the rat necessitated the use of one burr hole to allow adequte transmission of light through the cat's brain since the laboratory niroscope employed in this study utilized only a projector light bulb as its light source.

After positioning of the optics, two cannulas were inserted into the cisterna magna, one to instill "mock" CSF (38°C saline buffered to pH 7.0) and the second to measure intracranial pressure. Correct positioning of the cannulas was judged by the appearance of a drop of CSF at the cannula hub, and the recording of CSF pulsations when the cannula was connected to

a transducer. Intracranial pressure was increased by the instillation of "mock" CSF using an infusion pump and maintained constant at a given level by controlling the rate of infusion.

Prior to the start of an experiment, the cats were ventilated for ten minutes with a mixture of 95% O_2 - 5% CO_2. The resulting optical signals were arbitrarily defined as 100% oxidation. At the conclusion of each experiment the cats were ventilated with 100% N_2, and the resulting optical signals defined as 100% reduction (0% oxidation). All experimental data are expressed as percent oxidation based upon this full scale oxidation-reduction range.

EXPERIMENTAL PROTOCOL

After a 15-30 minute period during which the stability of the optical signals, intracranial pressure and arterial blood gases were confirmed, two cardiogreen dye curves were obtained and averaged to measure baseline blood flow. "Mock" CSF was then infused to increase the intracranial pressure to 20 mm Hg. Since it was possible to accomplish this without a change in the arterial pressure, the result was a reduction in cerebral perfusion pressure. A second period of 15 minutes then ensued to allow stabilization of all parameters as described above. The animals were then hyperventilated to produce respiratory alkalosis with arterial pCO_2's in the 20-25 mm Hg range. The animals were again allowed to stabilize and data recorded when the maximum reduction in intracranial pressure was achieved. Statistical significance was tested for by analysis of variance.

RESULTS

Technical problems precluded collection of complete data from three cats, and they were eliminated from further consideration. A typical record from one of the seven cats from whom data was collected is shown in Figure 1.

The alterations in mean arterial pressure, intracranial pressure, cerebral perfusion pressure and arterial blood gases for all seven cats are shown in Table I. By increasing the intracranial pressure gradually over ten minutes and not exceeding 20 mm Hg, the preparation proved stable and increases in arterial pressure (Cushing response) and plateau waves were avoided. Hyperventilation caused a predictable and significant reduction in intracranial pressure but little or no change in cerebral perfusion pressure since there was a decrease in arterial pressure concomitant with hyperventilation.

The expected reduction in cytochrome $\underline{a},\underline{a}_3$ and HbO_2 was noted at the time of increased intracranial pressure ($p < .01$), Figures 2-3. Flow, expressed as percent change from baseline, was also decreased by 7% (Figure 4). Hyperventilation, although decreasing intracranial pressure, was accompanied by a significant ($p < .001$) further reduction in cytochrome $\underline{a},\underline{a}_3$, redox state, and quantity of HbO_2 (Figures 2-3), an increase in Hb, and no significant change in HbT (Figures 5-6). There was no further reduction in blood flow, however, neither was there an improvement.

DISCUSSION

It is now quite clear that intracranial pressure monitoring in patients with severe head injury is an invaluable adjunct to patient management. One of the points we have previously made is that intracranial pressure measurement does not directly assess brain metabolism, but is routinely performed only because it represents the current "state of the art" best approximation of cerebral metabolism. In our earlier work,[4,5] in the process of establishing the accuracy of niroscopy as a means of assessing brain metabolism during periods of increased intracranial pressure, we also established, although indirectly, that a measurement of intracranial pressure did correlate very

well with metabolic events in the brain. These preliminary investigations were performed in a very rigidly controlled model in which, to prove a point, intracranial pressure was varied through a range far in excess of that seen clinically. The data collected in the present study in which intracranial pressure was varied between 0-20 mm Hg, values frequently encountered clinically, and then "treated" by hyperventilation, illustrate the shortcomings of intracranial pressure measurement as a reflection of brain metabolism.

Although mortality and morbidity from head injury has been reduced in our Trauma Unit with the advent of routine intracranial pressure monitoring, significant numbers of patients continue to die despite control of intracranial pressure by hyperventilation. The present data further illustrate that hyperventilation might not necessarily be in the best interests of the patient. Although intracranial pressure is decreased, it leads to a false sense of complacency since the decrease in intracranial pressure is accomplished by vasoconstriction with a further reduction in oxygen availability as evidenced by the increased reduction in HbO_2 and cytochrome $\underline{a},\underline{a}_3$ redox state. This was matched by a reciprocal increase in Hb, with little or no change in HbT. The effect of respiratory alkalosis is most apparent on the arterial side of the cerebral circulation, with little or no effect on the large venous sinuses which represent the greatest quantity of blood in the illuminated volume of tissue. Niroscopy in this model is thus relatively insensitive to total intracranial blood volume changes. The predominant metabolic effect of hyperventilation induced vasoconstriction would appear to be a reduction in HbO_2 indicating a reduced quantity of oxygenated blood on the arterial side of the circulation, with a concomitant failure of blood flow to improve as measured by cardiogreen, and a resulting reduction in oxygen availability

at the critical intramitochondrial level.

Several interesting questions are raised by this study which have therapeutic implications for the future. Although we have repeatedly focused in this discussion on intracranial pressure, it is the cerebral perfusion pressure which is the important determinant in providing oxygen and substrate to the brain. Rather than increasing perfusion pressure by attempting to lower intracranial pressure, what would be the effect of deliberately increasing arterial pressure, either as a sole therapeutic modality or in conjunction with hyperventilation? What would be the effect of increasing the arterial oxygen content rather than any attempt at manipulating cerebral perfusion pressure? The long-term effect of tissue hypoxia secondary to vasoconstriction is presumed to be acidosis with gradual reversal of the hyperventilation induced vasoconstriction and a return to the pre-hyperventilation state. What would be the effect of THAM or some other alkalizing agent in this model?

Although niroscopy as utilized in this study is obviously invasive, a more powerful niroscope using lasers as light sources has been developed[4], capable of collecting identical data non-invasively from humans. This machine is currently being tested. One of the initial purposes of this investigation was to further develop the concept of niroscopy as a non-invasive means of monitoring head injured patients. The current tole of niroscopy would appear to be as a screening device to follow patients at risk for increases in intracranial pressure. In this circumstance, both our previous work[1,2] and the data from this study indicate the non-invasive nature of niroscopy to be an advantage. However, in view of the results obtained during hyperventilation, and until such time as the answers to some of the above questions are known, it would appear that while we have made a case for the continued need for direct

assessment of brain metabolism as opposed to the indirect assessment provided by intracranial pressure monitoring, reduction in intracranial pressure and improvement in cerebral perfusion pressure might better be accomplished by ventriculostomy and drainage of CSF. This negates the non-invasive advantage of niroscopy.

In summary, the data collected in this study point up the advantages of niroscopy in providing data not heretofore available during periods of increased intracranial pressure. They further illustrate the fallacy of treating the symptoms of increased intracranial pressure rather than directly addressing the basic metabolic problem, while, at the same time, providing a possible explanation for the continued morbidity and mortality in head injured patients despite control of increased intracranial pressure through hyperventilation. Knowledge of the effect of intracranial pressure on cytochrome function and the further deterioration after hyperventilation raises several important issues for speculation concerning the possibility of improved therapy in the future.

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TABLE I

	Baseline	Increased ICP	Hyperventilation
MAP	98.6	97.1	87.1
s.e.m.	(±5.084)	(±5.3)	(±7.47)
ICP	3.1	18.4	15.3
s.e.m.	(±1.0)	(±0.4)	(±0.9)
CPP	94.7	79.0	72.2
s.e.m.	(±5.3)	(±5.2)	(±4.3)
pCO_2			
s.e.m.	33.2	34.4	24.2
	(±0.8)	(±0.5)	(±0.1)
pH	7.3	7.29	7.66
s.e.m.	(±0.03)	(±0.01)	(±0.03)

Mean (±) standard error (s.e.) and number of observation (n) for mean arterial pressure (MAP), intracranial pressure (ICP), cerebral perfusion pressure (CPP, arterial pH and pCO_2.

LEGEND - Figure 1

Representative recording from one cat (redrawn) illustrating the overall findings of the study. Note the reduction of cytochrome $\underline{a},\underline{a}_3$ concomitant with the rise in intracranial pressure, and a further reduction as well as a decrease in HbO_2 with hyperventilation. Not shown on this tracing are the flow signal or Hb signal.

LEGEND - Figure 2

Reduction in cytochrome $\underline{a},\underline{a}_3$ with increased intracranial pressure and further reduction with hyperventilation. n - 7; error bars are standard error.

LEGEND - Figure 3

Reduced quantity of HbO_2 with increased intracranial pressure and further reduction with hyperventilation. n = 7; error bars are standard error.

LEGEND - Figure 4

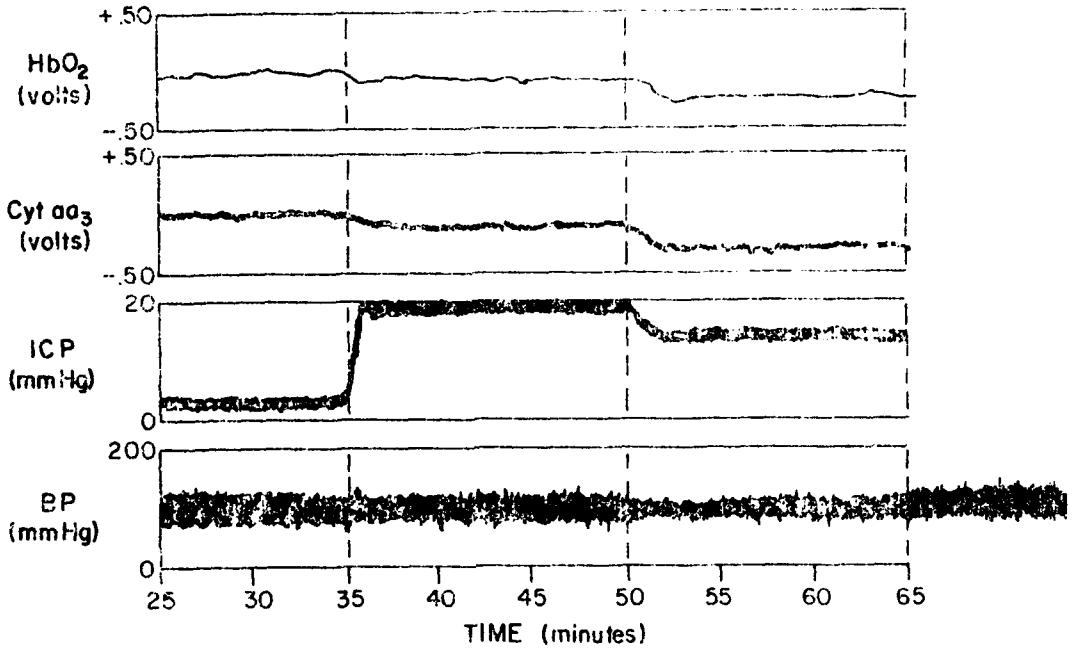
Reduction in cardiogreen derived perfusion with increased intracranial pressure. No improvement with hyperventilation. n = 7; error bars are standard errors. Data are expressed as percent change from baseline which is arbitrarily 100%.

LEGEND - Figure 5

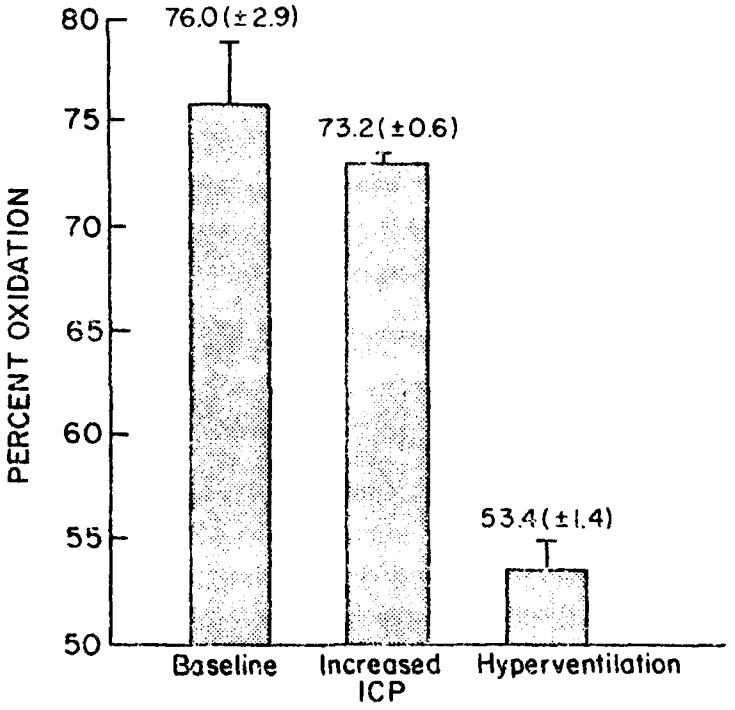
Increase in Hb with elevated intracranial pressure with a further increase after hyperventilation. n = 7; error bars are standard error.

LEGEND - Figure 6

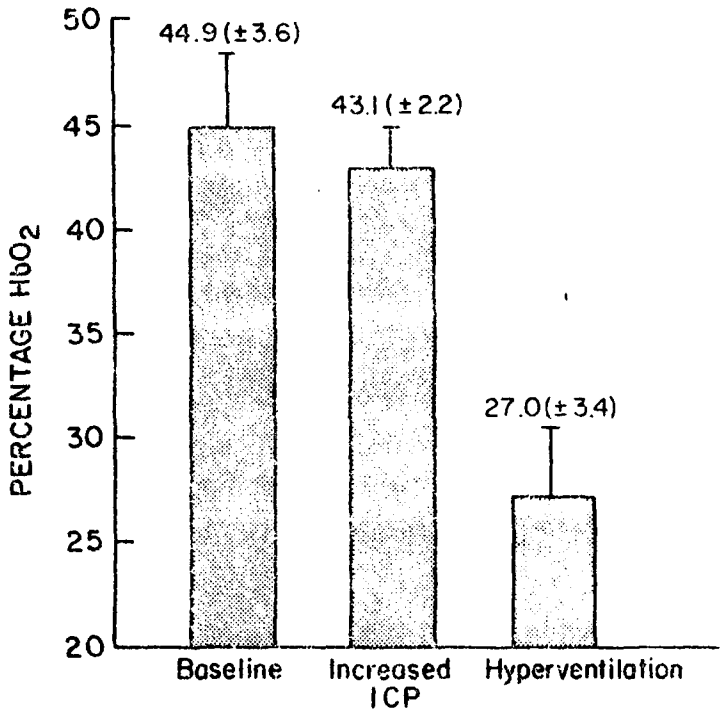
Lack of change in HbT despite increased intracranial pressure and hyperventilation. n = 7; error bars are standard errors. Baseline is arbitrarily defined as 100% and subsequent levels relative to this.


+.50
HbO_2
(volts)
-.50
+.50
Cyt aa_3
(volts)
-.50
20
ICP
(mmHg)
0
200
BP
(mmHg)
0
25
30
35
40
45
50
55
60
65
TIME (minutes)

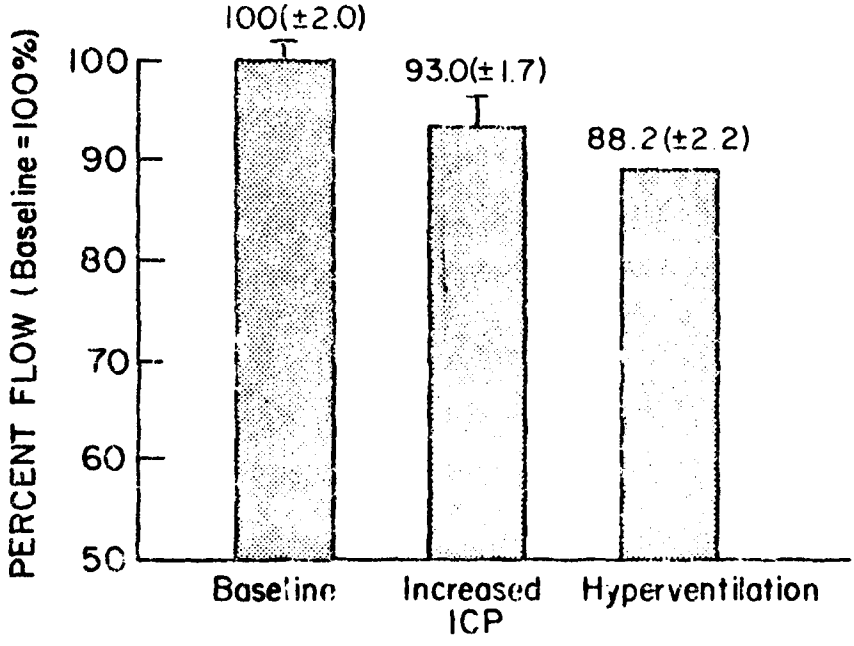
CYTOCHROME a,a_3 REDOX STATES DURING INCREASED INTRACRANIAL PRESSURE AND HYPERVENTILATION

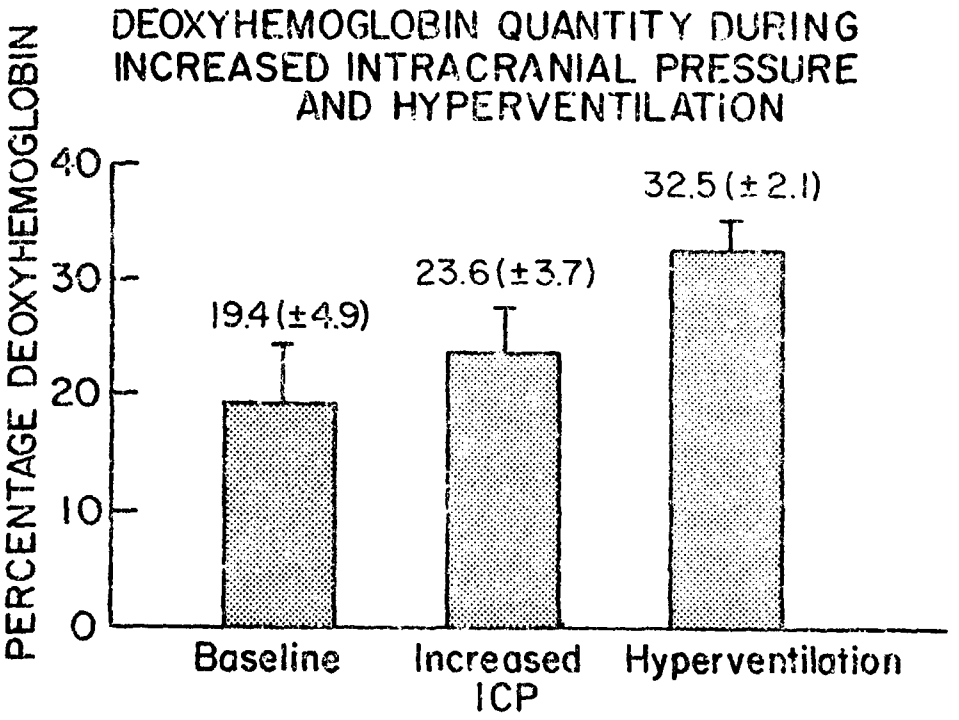


OXYHEMOGLOBIN LEVELS DURING INCREASED INTRACRANIAL PRESSURE & HYPERVENTILATION

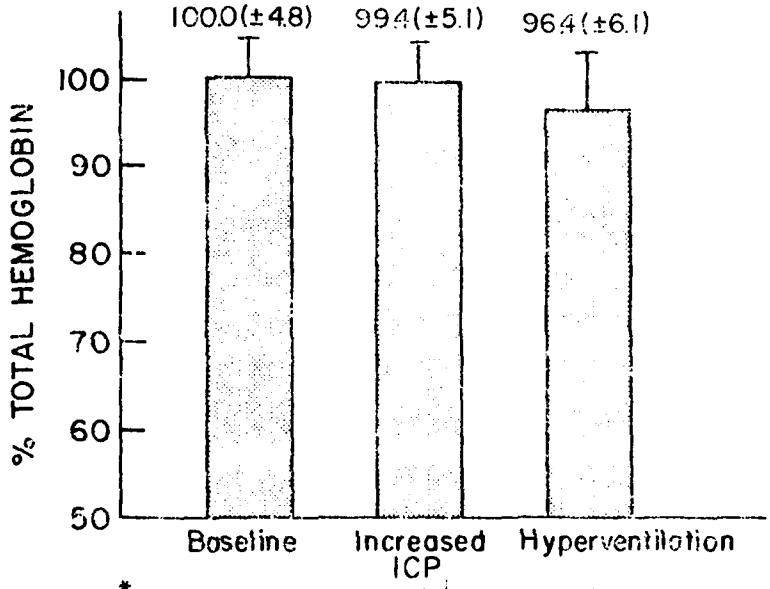


CEREBRAL BLOOD FLOW FOLLOWING
INCREASED INTRACRANIAL PRESSURE
AND HYPERVENTILATION




DEOXYHEMOGLOBIN QUANTITY DURING
INCREASED INTRACRANIAL PRESSURE
AND HYPERVENTILATION
PERCENTAGE DEOXYHEMOGLOBIN
40
30
20
10
0
19.4 (±4.9)
23.6 (±3.7)
32.5 (±2.1)
Baseline
Increased
ICP
Hyperventilation

TOTAL HEMOGLOBIN* QUANTITY DURING INCREASED INTRACRANIAL PRESSURE AND HYPERVENTILATION



*New Baseline level is set arbitrarily as 100 % with all other quantities relative to this.

HIGH FREQUENCY VENTILATION IN RABBITS WITH RESPIRATORY INSUFFICIENCY

High Frequency Ventilation in ARDS

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ABSTRACT

Treatment of respiratory insufficiency using continuous positive pressure ventilation with positive end-expiratory pressure (CPPV) is often associated with high airway pressures and large tidal volumes resulting in parenchymal damage and an exacerbation of ventilation/perfusion missmatch. High frequency jet ventilation and high frequency oscillation purportedly provide adequate ventilation and might preclude these harmful side-effects. Few data exist comparing these methods in a model of respiratory insufficiency.

Respiratory insufficiency was produced in three groups of six rabbits by 15 pulmonary lavages with saline (35 $ml.kg^{-1}$) to remove surfactant, following which ventilation for the subsequent five hours was: Group I, CPPV with a frequency of 60 bpm, and a minute volume of 400 $ml.min^{-1}.kg^{-1}$, Group II, oscillatory ventilation with a loudspeaker-system delivering a tidal volume of 6-8 ml at a frequency of 5 Hz, and Group III, jet ventilation with volumes of 6-8 ml at a frequency of 5 Hz. All groups were ventilated with a PEEP of 10 cm H_2O and a F_iO_2 of 1.0. Arterial blood samples were taken every hour.

All three methods provided adequate oxygenation without important differences. The arterial pCO_2 rose in all three groups owing to the seriousness of the respiratory insufficiency created. This rise was the highest with oscillatory ventilation. Three of the six rabbits deteriorated after three hours of jet ventilation and died with elevated pCO_2's and low pO_2's with bloody edema coming out of the trachea. Because of this apparent damaging effect of jet ventilation and because oscillatory ventilation achieved the same gas exchange but at lower airway pressures as compared

to jet ventilation and CPPV, we feel oscillatory ventilation to be superior over both jet ventilation and CPPV for application in respiratory insufficiency.

INTRODUCTION

Continuous positive pressure ventilation with positive end-expiratory pressure (CPPV) and/or intermittent mandatory ventilation with positive end-expiratory pressure (IMV-PEEP) continue to be the main forms of ventilatory support for patients with adult respiratory distress syndrome (ARDS). Despite substantial improvement in survival brought about by the introduction of these therapeutic modalities, patients continue to die either directly or indirectly as a result of ARDS. Whether the treatment contributes to further pulmonary damage and eventual death is not clear but the large minute volumes and high airway pressures associated especially with CPPV have been blamed for difficulty in maintaining cardiac output, fluid retention, pulmonary parenchymal damage, and further exacerbation of ventilation/perfusion missmatch (3,6).

When ventilation is achieved utilizing periodic insufflation of a volume of gas in excess of deadspace, its distribution is largely a function of lung compliance with the gas tending to go to the most compliant parts of the lungs. Thus, in ARDS, there is a very inhomogeneous distribution of gas, with a worsening of the already existing ventilation/perfusion missmatch. Further missmatch occurs if the alveolar pressure exceeds capillary pressure, causing shunting of blood to less ventilated parts of the lungs and increasing pulmonary vascular resistance. The local hyperventilation thus created may also lead to lung tissue becoming locally alkalotic, which may in turn play a role in further tissue damage (4).

By ventilating patients with ARDS using small tidal volumes at a high frequency (HFV) several of the harmful side effects of CPPV might be circumvented owing to the absence of high airway pressures associated with CPPV.

High frequency ventilation may also result in a more homogeneous distribution of the inspiratory gas since distribution is less a function of pulmonary compliance and more a function of the conductive properties of the airways. HFV may also prevent the lung tissue from becoming locally alkalotic secondary to local hyperventilation because a gradient for the CO_2-concentration is maintained between the alveoli and the trachea with theoretical preservation of tissue pH.

There are two methods of accomplishing high frequency ventilation: administering gas in to the trachea in the form of small puffs as in jet ventilation or by imposing a high frequency oscillation on a continuously insufflated gas flow. In the investigation reported here these two methods of high frequency ventilation are compared with each other and with CPPV in a model of respiratory insufficiency designed especially to test for the ability to eliminate CO_2.

MATERIALS AND METHODS

Adult chinchilla or mixed breed rabbits (2.8 - 3.4 kg) were anesthetized with sodium pentobarbital (Nembutal^R, 30 $mg.kg^{-1}$ i.v.). After tracheostomy the rabbits were heparinized with an initial dose of 2 $mg.kg^{-1}$. Additional heparin (1 $mg.kg^{-1}$) and sodium pentobarbital (6 $mg.kg^{-1}$) were given every hour. An arterial cannula was placed in one carotid artery for pressure monitoring and the obtaining of blood samples. A fiber optic catheter was inserted in the other carotid artery for continuous measurement of the hemoglobin saturation (Schwartzer Oxymeter IVH-3). The rabbits were then paralyzed with pancuroniumbromide (Pavulon^R (0.1 $mg.kg^{-1}$)) and ventilated with a mixture of 75% O_2 and 25% N_2O with a PEEP of 5 cm H_2O and at a rate of 60 min^{-1}. The tidal volume was adjusted to achieve an arterial pCO_2 within the normal range. The tracheal pressure was measured with a fluid

filled pressure transducer (Statham P23dB) and a 16 G catheter inserted directly in the trachea.

Pulmonary lavage was next performed to remove surfactant from the alveolar lining layer using a modification of the technique described by Lachman (5). Each lavage consisted of normal saline at 38° C instilled intratracheally to a volume of 35 $ml.kg^{-1}$ or to an intratracheal pressure of 40 cm H_2O, whichever occurred first. Each lavage required 20 seconds to perform and the procedure was repeated 15 times at five minute intervals.

In a series of preliminary experiments it was determined that to adequately ventilate the rabbits during the lavage procedure it was necessary to increase the inspired oxygen concentration to 100%, the PEEP to 10 cm H_2O and the minute volume to 400 $ml.min^{-1}kg^{-1}$.

After the last lavage and while still on CPPV the arterial pressure, heart rate, peak inspiratory pressure, arterial pO_2, pCO_2, and pH were measured. The rabbits were then allocated to one of three treatment groups and the above measurements were repeated after ten minutes and after each hour for five hours.

Group 1-CPPV

The rabbits (n = 6) in this group continued to be ventilated with a F_iO_2 of 100%, at a frequency of 60 bpm with 10 cm H_2O PEEP and a minute volume of 400 $ml.min^{-1}.kg^{-1}$.

Group 2-Oscillatory Ventilation With PEEP

The rabbits (n = 6) in this group were connected to a loudspeaker system oscillating at 5 Hz. The oscillatory volume delivered by this system was measured in vitro to be 6-8 ml. Oxygen was insufflated into the trachea through a small lumen in

the wall of the tracheostomy tube. Mixed gas containing CO_2 was withdrawn from the tracheostomy tube through the loudspeaker housing and through thin tubing by the pump of a CO_2 analyzer (Fig. 1). The CO_2-concentration of the gas mixture was measured and the quantity of the removed CO_2 calculated by multiplying the O_2-concentration by the gas flow. By balancing the O_2-inflow and the gas outflow a mean airway pressure of 10 cm H_2O was created. The pressures on both sides of the cone of the loudspeaker were equalized by connecting the spaces on both sides by means of thin tubing. Every six minutes the lungs were insufflated to a pressure of 20 cm H_2O in order to maintain the compliance and the FRC (1).

Group 3-Jet Ventilation With PEEP

The rabbits (n = 6) in this group were ventilated by administering small jets of oxygen at a frequency of 5 Hz with an inspiration time percentage of 10-20% by means of a solenoid valve system through a thin polyethylene tube placed in the tracheostomy tube with the tip near the carina. An expiration tube connected to the tracheostomy tube was placed under water to create an end-expiratory pressure of 10 cm H_2O.

RESULTS

Oscillatory ventilation provided for adequate oxygenation (Fig. 2a), but failed to remove sufficient quantities of CO_2 as shown by the gradual increase in the arterial pCO_2 (Fig. 2b), an increase which did not differ significantly from the increase in pCO_2 resulting from conventional ventilation.

Jet ventilation resulted in a slightly lower arterial pO_2 and after

the third hour post lavage three out of the six rabbits in this group deteriorated rapidly and died. After death five to ten ml of bloody fluid could be aspirated from the trachea. The other three rabbits survived the five hour experimental period but with a steadily decreasing arterial pO_2. The arterial pCO_2 remained within the normal range for all Group III rabbits. Note, data shown for Group III after three hours are derived from a skewed population of survivors and preclude meaningful statistical comparison with Groups I and II.

The peak inspiratory pressures measured in the trachea were slightly higher during jet ventilation than during conventional ventilation, whereas the maximal pressures during oscillatory ventilation were only a few cm H_2O higher than the 10 cm H_2O mean tracheal pressure (Fig. 2c). A typical example of the pattern of the tracheal pressure during the three ventilatory modes is shown in Fig. 3.

Neither arterial blood pressure nor heart rate changed significantly as compared with prelavage values and did not differ between the three groups.

DISCUSSION

Of paramount interest is the failing of jet ventilation as a treatment modality in this experimental model of respiratory insufficiency. Evidently jet ventilation as employed in this study had a damaging effect on the lung tissue as demonstrated by the death of three rabbits, the inadequate oxygenation of the remaining three in the latter two hours of the experiment, and the abundant pulmonary edema. Neither conventional ventilation nor oscillatory ventilation appeared to have this deleterious effect. Ventilation by the jet method is possibly more effective than oscillatory and conventional methods in terms of arterial pCO_2, which was maintained within normal limits throughout the experiment.

When oscillatory ventilation was initiated, the arterial pO_2 showed an improvement compared to conventional ventilation. Although cardiac output was not measured, the equal and normal arterial pressures in the three groups make differences in cardiac output unlikely. Thus improvement in the arterial pO_2 is presumably a result of a decrease in intrapulmonary shunt. This intrapulmonary shunt is most probably caused by atelectasis as a result of the almost complete washout of surfactant out of the alveolar lining layer and may be decreased by recruitment of atelectatic alveoli resulting from the periodic inflations performed as a part of the oscillatory ventilation protocol.

The gradual increase in pCO_2 which occurred during oscillatory ventilation is presumably caused by the small capacity of the high frequency ventilator, which had nevertheless ample capacity to ventilate normal rabbits. The CO_2-retention can be estimated roughly to be 0.2 $ml.min^{-1}$ for a 3 kg rabbit with an estimated blood volume of 170 ml. This represents only about 1% of the normal CO_2-production. A rise in the arterial pCO_2 at the end of the experimental period was also noted with conventional ventilation, demonstrating the seriousness of the respiratory insufficiency created by repeated lung lavage.

Repeated lung lavage was chosen to create a model of respiratory insufficiency for this study because it creates a reproducible state of respiratory insufficiency which is stable over a period of at least several hours without major hemodynamic disturbances. Pilot experiments showed that the experimental lesion thus created makes it particularly difficult to eliminate CO_2, a known weakness of high frequency ventilation, therefore we regard lavage as an adequate choice for the purpose of comparing two methods of high frequency ventilation with conventional ventilation as

a reference.

The decision to define conventional ventilation for the purpose of this study as CPPV, with a frequency of 60 breath.min^{-1}, and a minute volume of 400 ml.min^{-1}.kg^{-1} with a PEEP of 10 cm H_2O was based upon defining an upper limit of pressures and volumes, which, transposed to human equivalent values, would cause in our opinion most physicians to become concerned about pulmonary damage and below which many physicians would have little cause for alarm or reason to seek alternate forms of respiratory support. The decision to ventilate with 100% oxygen was made to simplify the interpretation of the arterial pO_2. Having defined conventional ventilation the grade of respiratory insufficiency was then adjusted in a series of pilot experiments by increasing the number of lavages to produce a degree of difficulty in oxygenation and CO_2 elimination such that CPPV as applied in this study could just maintain the arterial pO_2 and pCO_2 in an acceptable range as reflected by the post lavage data.

The frequency of 5 Hz for oscillatory ventilation was selected on the basis of pilot experiments in which we found this frequency to give the best CO_2 elimination with the ventilator system used. The amplitude of oscillation at this frequency, about 6-8 ml, is less than the anatomical deadspace of a rabbit. In pilot experiments with jet ventilation it was found that CO_2 elimination was best also at 5 Hz.

In all three methods a "PEEP" of 10 cm H_2O was applied to prevent atelectasis. Since in the model of respiratory insufficiency used in this study continuous positive airway pressure is necessary to keep the alveoli from collapsing. This pressure will be at least partly countered by the increased recoil forces of the lung tissue and will therefore have less hemodynamic impact than the same pressure in normal lungs. This was

confirmed in pilot experiments with normal rabbits where a PEEP of 10 cm H_2O resulted in serious decrease of the arterial blood pressure. Since in ARDS the amount of surfactant in the alveolar lining layer is less than in normal lungs or is partly deactivated by plasma proteins present in alveolar edema (3), one would expect that a moderate continuous positive airway pressure would help to improve gas exchange by increasing FRC without any danger of impeding venous return. In this light it is remarkable that some authors reporting on HFV applied in respiratory insufficiency do not use continuous positive airway pressure (2).

In all three methods of ventilation employed in this study the ventilatory pattern was superimposed on the constant airway pressure of 10 cm H_2O. This resulted for oscillatory ventilation in a mean airway pressure as low as 10 cm H_2O, whereas the peak and mean airway pressures for both jet and CPPV were higher and not significantly different from each other. Therefore the damaging effect of jet ventilation may well be due to the steepness of the pressure curves which in CPPV, is much less, while in oscillatory ventilation the curves are much lower.

Because of this damaging effect of jet ventilation and because oscillatory ventilation achieved the same gas exchange as jet ventilation and CPPV, but at lower airway pressures, this method may be preferred for application in respiratory insufficiency.

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FIGURE 1

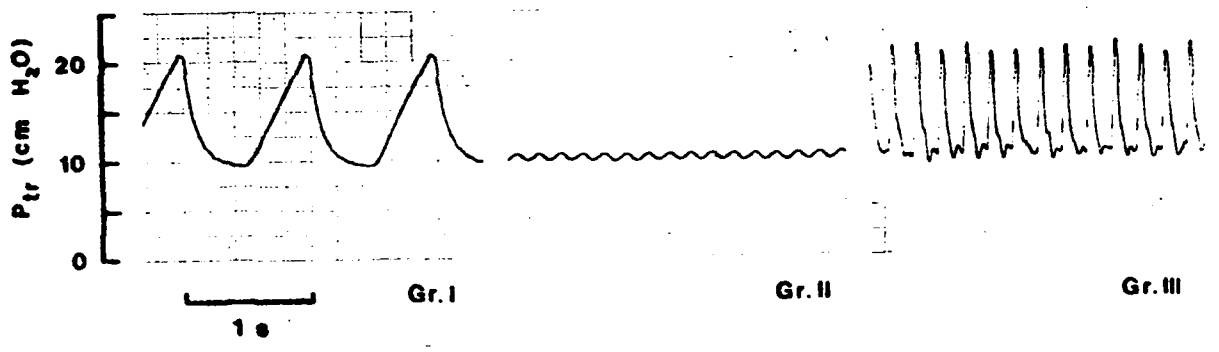
Diagram of the loudspeakder system used for oscillatory ventilation.

FIGURE 2

The arterial pO_2 (a), the arterial pCO_2 (b), and peak inspiratory pressure (c) post lavage on CPPV and after 10 minutes, 1, 2, 3, 4, and 5 hours on CPPV (CV), on oscillatory ventilation (OV), and jet ventilation (JV).

FIGURE 3

Typical examples of the pattern of the tracheal pressure on CPPV (Gr. I), on oscillatory ventilation (Gr. II), and jet ventilation (Gr. III).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Gr. I
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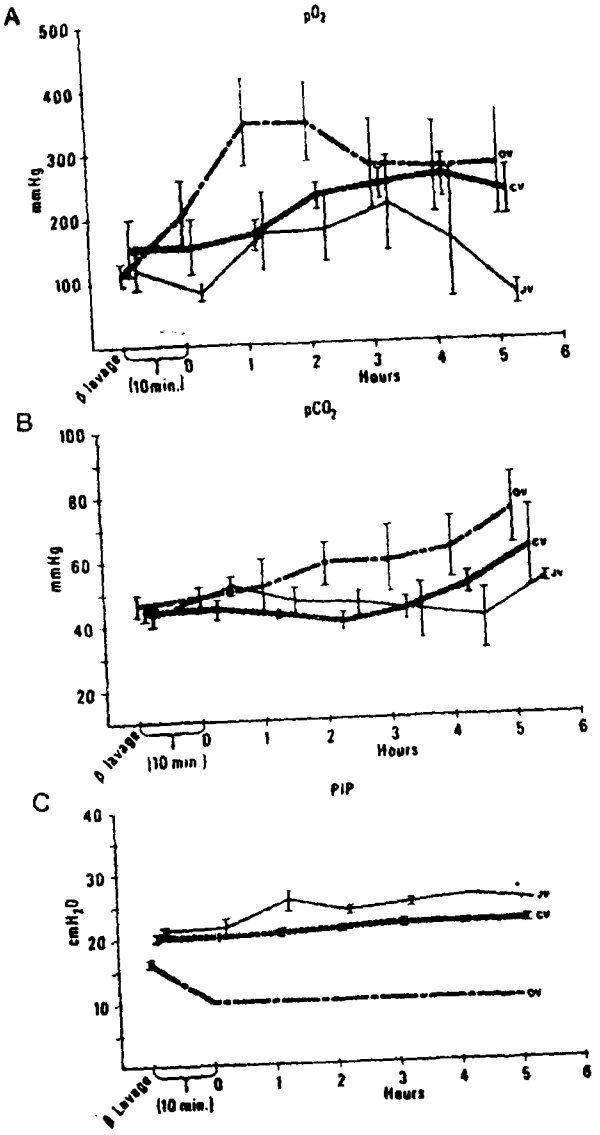
Gr. III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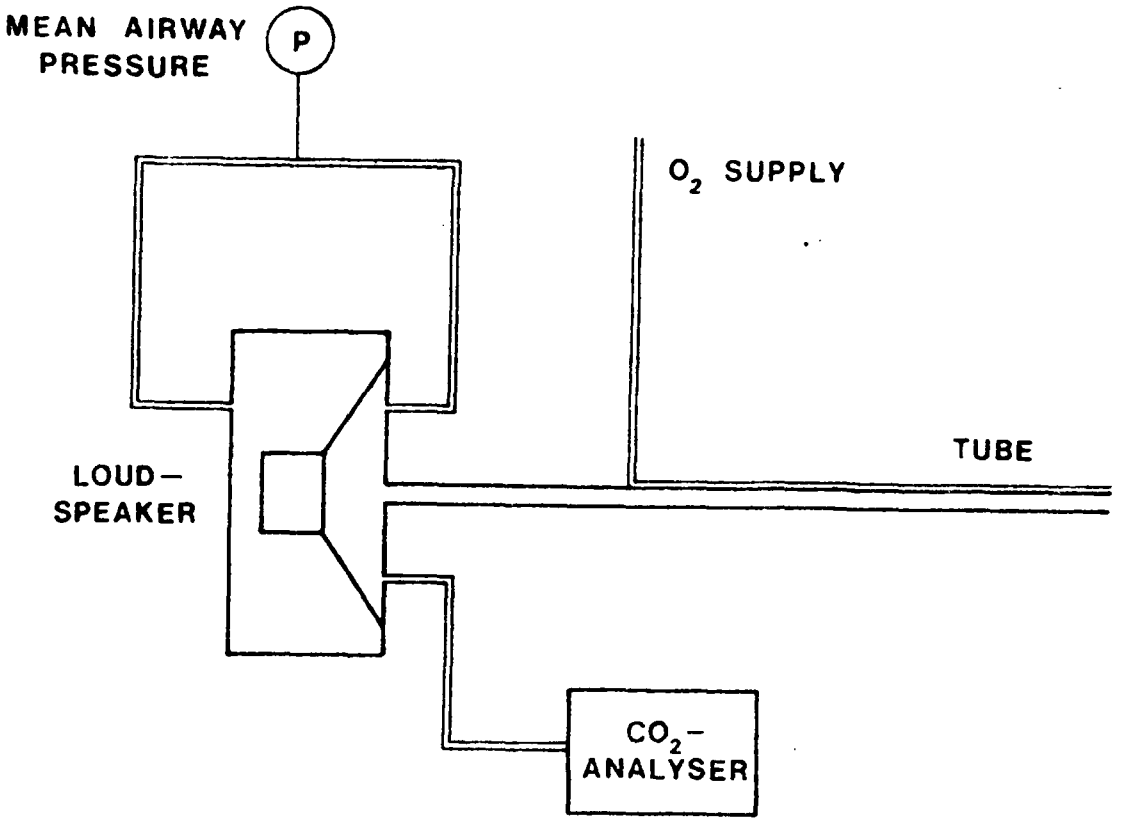
MEAN AIRWAY PRESSURE
P
O_2 SUPPLY
TUBE
LOUD–SPEAKER
CO_2–ANALYSER

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NEAR INFRARED SPECTROPHOTOMETRY: A NON-INVASIVE METHOD FOR ASSESSING THE EFFECTS OF CHANGES IN INTRACRANIAL PRESSURE ON BRAIN METABOLISM IN CATS. Charles B. Cairns, Drew Fillipo, Herbert J. Proctor. Trauma Section, Department of Surgery, University of North Carolina, Chapel Hill, NC 27514

We report two experiments designed to clarify the role of in vivo near infrared spectrophotometry (niroscopy) for directly measuring the effects of changes in intracranial pressure (ICP) on brain metabolism. Cytochrome a,a_3 redox state, oxyhemoglobin, and deoxyhemoglobin were continuously monitored by niroscopy in adult female cats during experimentally induced increased ICP. In the first experiment (N=10), ICP was markedly increased in 40 mmHg increments from baseline to arterial systolic pressure by cisterna magna infusion of saline. In the second experiment (N=10), a more clinically relevant model was adopted. Subarachnoid infusion of a "mock" CSF solution produced a moderately elevated ICP (18.5 ± 0.9 mmHg). ICP was monitored via a cisterna magna catheter. The results of both experiments indicate that changes in ICP correlated with a reduction of cyt. a,a_3 redox state ($p<.01$), a monotonic decrease in HbO_2 and a monotonic increase in Hb. These studies suggest the use of niroscopy as a sensitive, non-invasive method for directly monitoring brain metabolic activity during episodes of increased intracranial pressure.
(Supported in part by ONR Contract #N00014-79-C-0852 and the Holderness Foundation)

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CEREBRAL HIGH ENERGY PHOSPHATE METABOLISM AFTER HYPOXIC-HYPOTENSION: THE ROLE OF CA++ BLOCKERS. G. William Palladino, Herbert J. Proctor, Richard Sanders. Trauma Section, Department of Surgery, University of North Carolina, Chapel Hill, NC 27514

Failure of cerebral cortical high energy phosphate production after hypoxic-hypotension results both from mitochondrial defects and areas of "no reflow". Ca++ blockers might act on either or both of these sites. Thirty rats were subjected to 30 minutes of combined hypoxia (FIO_2 = 7.5%) and hemorrhagic hypotension (MAP = 30 mmHg), and then resuscitated by reinfusion of all shed blood, an equal volume of saline, and restoration of FIO_2 = 30%. Group I received blood and saline alone; Group II received in addition .2 mg/Kg verapamil and Group III received in addition 10 ug/Kg nifedipine. Rats were sacrificed by liquid nitrogen freezing of their brain 20 and 120 minutes after treatment group allocation/resuscitation. Cerebral cortices were assayed for creatine phosphate (CP), adenosine tri-phosphate (ATP) and lactate (L).

Significantly greater ($p<.01$) I vs. III) concentrations of CP and ATP resulted 20' and 120' after resuscitation in nifedipine treated animals, while no improvement (I vs. II) was noted for verapamil. Blood pressure was restored equally in the three groups, and in view of the more potent vasodilator effects of nifedipine as opposed to verapamil, our results are possibly explainable on the basis of improved cerebral cortical blood flow.

EFFECT OF ETHANOL ON LACTIC ACIDOSIS IN EXPERIMENTAL HEMORRHAGIC SHOCK

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ABSTRACT

Many victims of trauma who have hemorrhagic shock are also intoxicated. Ethanol could worsen the severity of shock and decrease the amount of blood loss necessary to reach or maintain the shock state, perhaps by increasing lactic acidosis. We examined the effect of ethanol on lactic acidosis in a group of rats that were intoxicated, then placed into a state of hemorrhagic shock (MAP = 40 mmHg). These animals were compared to a control group that were in a similar state of hemorrhagic shock but not intoxicated. The volumes of blood necessary to reach and maintain the predetermined model state of shock for two hours in each group were also measured. The animals were paralyzed and placed on controlled ventilation. The ethanol produced an expected baseline lactic acidosis, and it took significantly less blood volume loss to keep the intoxicated group in shock. However, during shock there was no significant difference in the state of lactic acidosis. These results suggest that acute ethanol intoxication made the animals more sensitive to hemorrhage. This effect was not mediated by an increase in lactic acisosis in our model.

Introduction

Acute ethanol intoxication is involved in at least 40% of injured patients admitted to emergency departments,[1,2] and many victims of blunt and penetrating trauma are in shock.[3] Whether the effect of acute ethanol intoxication is protective or detrimental in seriously injured patients has not been conclusively determined.[4,5] Because of the multiplicity of variables effecting the clinical status of the polytrauma victim, it is extremely difficult to develop a reliable objective relationship between ethanol intoxication and clinical outcome. However, we suspected that ethanol contributed to the severe metabolic acidosis seen in the severely injured patient. Studies by Malt and Baue[6] and Gettler and Albritten[7] in both awake and anesthetized dogs subjected to hemorrhage suggest that impaired ventilation from intoxication may prevent an appropriate respiratory response to metabolic acidosis. Since the oxidation of ethanol raises the NADH:NAD ratio and causes lactate accumulation, the contribution of ethanol to lactic acidosis in hemorrhagic shock could involve more than simple ventilatory depression. This possible effect of ethanol on lactic acidosis from hemorrhagic shock has not previously been studied.

Our study was done to determine the effect of acute ethanol intoxication on the lactic acidosis resulting from experimental hemorrhagic shock in rats under controlled ventilation. We also examined the effect of intoxication on the blood volume loss necessary to

maintain a shock state.

Materials and Methods

Animals and Procedures

A total of 16 male Sprague-Dawley rats weighing approximately 300 grams were divided between an intoxicated experimental group and a non-intoxicated control group. The animals were fasted 18 hours prior to the experiment. One hour prior to hemorrhage the animals were lightly anesthetized with thiopental sodium intraperitoneally. The group to be intoxicated received 30 mg/kg thiopental sodium and the non-intoxicated control group received 50 mg/kg. A solution of 20% ethyl alcohol in a dose of 3 gm/kg was then administered via gastric tube. The control group was given an equivalent volume of 0.9%. A tracheostomy was performed and the animals were placed on a rodent ventilator using room air. Both femoral arteries and a femoral vein were cannulated using PE 50 and PE 50-10 catheters. This allowed for arterial bleeding to produce hemorrhagic hypotension, arterial blood pressure monitoring, anaerobic blood sampling ($PaCO_2$, PaO_2, pHa) and drug infusion. All catheter lengths were the same to assure accurate blood volume measurement. Tubocurarine chloride (0.1 mg/kg) was given intravenously, and the ventilator was adjusted so that arterial PCO_2 ranged from 35 to 40 mm Hg and the arterial PO_2 was greater than 90 mm Hg. The animals were given 200 units of heparin intravenously.

At one hour post-ethanol administration, arterial blood for base-

line measurement of blood gases, serum ethanol and serum lactate was drawn. Controlled hemorrhage to induce a standard state of shock began immediately thereafter. The technique consisted of steady withdrawal of blood until the mean arterial pressure was reduced to 40 mm Hg. Duration of initial acute hemorrhage was less than 3 minutes. Thereafter, blood was periodically withdrawn to maintain a mean arterial pressure of 40 mm Hg. Blood was taken for blood gas analysis every half-hour, and at 1 and 2 hour intervals for measurement of serum ethanol and lactate. The initial and total shed volumes were recorded. The initial shed volume was the volume loss necessary to reduce mean arterial pressure to 40 mm Hg. The total shed volume was the initial shed volume plus the volume necessary to maintain the hemorrhagic shock state. After two hours in shock, the rats were sacrificed with a lethal dose of potassium chloride.

Blood Gas Analysis

All arterial measurements of PCO_2, PO_2, and pH were done on an Instrumentation Laboratory, Inc ph/Gas Analyzer.

Serum Ethanol and Lactate Determinations

Serum ethanol levels were determined by gas chromatography.[8] Serum lactate levels were determined by a centrifugal analyzer kinetic procedure.[9]

Statistical Analysis

The significance of all differences was assessed with student's

t-test, and data are expressed as means ± SEM.[10]

Results

Serum Ethanol Concentrations

At the time of the onset of hemorrhage, one hour after dosing, the average ethanol level was 244 mg% in the intoxicated rats (Figure 1). While the average ethanol concentration decreased over the two-hour course of the experiment, it still remained well above 150 mg%.

Acidosis During Shock

Immediately prior to hemorrhage, the intoxicated group was significantly more acidotic than the non-intoxicated control group ($P<0.02$) (Figure 2). This initial difference did not persist as both groups became increasingly acidotic. The acidosis became severe, yet there was no significant difference in the mean pHs of the two groups during shock. Serum lactate concentrations correlated with changes in arterial pH in the two groups (Figure 3). While the serum concentrations of lactate was significantly greater in the intoxicated group before the shock state was induced ($P<0.05$), at 1 and 2 hours in shock both groups had similar lactate levels.

Blood Volume Loss

There was no significant difference in the initial shed volume between the two groups (Figure 4). However, the total shed volume was significantly less in the intoxicated group (21.0 ml/kg) than the control group (25.0 ml/kg) ($P<0.001$).

Discussion

These results suggest that in the intoxicated rat under controlled ventilation, ethanol does not contribute to the lactic acidosis resulting from very severe hemorrhagic shock over the time period studied. This is in contrast to our hypothesis that the metabolism of ethanol might inhibit lactate clearance in hemorrhagic shock. It is well accepted that the metabolism of ethanol begins by oxidation with NAD in the liver. The resultant increase in the ratio of NADH to NAD shifts the equilibrium for lactate dehydrogenase toward lactate. Ethanol intoxication alone shifts this equilibrium toward lactate and an accumulation of lactate accompanies the increase of NADH.[11] It has been suggested [12] that the clearance of a lactate load from the blood following ethanol ingestion is significantly impaired in the diabetic patient. Therefore, one might expect that intoxication combined with hemorrhagic shock would produce a more severe acidosis than hemorrhagic shock alone. This effect was not seen in this study.

The lack of an effect of ethanol on the lactic acidosis in hemorrhagic shock might be due to the severity of shock produced in this model. The high levels of lactate resulting from anaerobic glycolysis could have overshadowed the shift in lactate/pyruvate ratios caused by the effects of ethanol oxidation on the ratio of NADH to NAD. Alternatively, the relatively short duration of intoxication before induction of the shock state may not have allowed sufficient NADH accumulation.

The results of this study do suggest that acute ethanol intoxication made the rats more sensitive to hemorrhage. This observation has been made before in a group of intoxicated dogs[13] and was thought to be secondary to the vasodilatory effect of ethanol. However, in contrast, Knott and associates[14] concluded that acute ethanol intoxication did not effect hemorrhagic shock in dogs.

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Legends for Illustrations

Figure 1. Average ethanol levels in the intoxicated rats.

Figure 2. Changes in arterial pH during shock. The pHs were corrected to a pCO_2 of 40 mm Hg. Asterisk denotes $P<0.02$.

Figure 3. Changes in levels of serum lactate during shock. Asterisk denotes $P<0.05$.

Figure 4. Shed blood volumes. Asterisk denotes $P<0.001$.

MATERNAL AND FETAL EFFECTS OF EXCHANGE TRANSFUSION WITH A RED CELL SUBSTITUTE.

Robert C. Cefalo, John W. Seeds, Herbert Proctor, Francis Johsis, Chapel Hill, NC

The fluorocarbon emulsion Fluosol-DA (20%) is an acellular O_2 carrier. Recent clinical reports have demonstrated the potential usefulness of Fluosol-DA as temporary red cell substitute. Perfluorochemical emulsions are known to maintain blood pressure and transport oxygen in laboratory animals that have undergone exchange transfusion to a hematocrit of 1%. The maternal cardiodynamics and fetal cerebral oxygenation responses to a total isovolumetric exchange transfusion with Fluosol-DA were studied in two groups of near term ewes.

Via hysterotomy incision the fetal head was exteriorized and a fiber optic bundle and photomultiplier tube placed against the cranium. The internal jugular vein of the fetus was catheterized. Uterine blood flow, maternal blood and pulmonary artery pressures were measured. Serial maternal and fetal blood gases and pH, hematocrits and fluorocrits (the volume of circulating perfluorochemical) were obtained. The infrared spectrophotometric method allowed continuous assessment of fetal oxygenation, recorded as relative changes in fetal oxidized and reduced hemoglobin.

Animals in Group I underwent a near total isovolemic exchange of Fluosol-DA for maternal whole blood via a femoral artery and vein using an IBM-2997 continuous flow blood cell separator. Animals in Group II had their red blood cells removed and their plasma along with Ringers Lactate replaced isovolumetrically to the ewe.

In Group I, while receiving 100% oxygen and being exchanged with Fluosol-DA, maternal arterial PO_2 averaged 350-400 torr and the maternal O_2 content increased during the maternal exchange with no change in fetal pH, PCO_2, or

hematocrit. Maternal cardiodynamics remained stable except for a 30-40% increase in cardiac output. During the exchange the maternal hematocrit decreased by 75-80%.

The maternal fluorocrit increased to an average of 9-10 volume percent. Throughout the exchange the quantity of fetal brain oxyhemoglobin as estimated from infrared transmittance increased as did the fetal PO_2 and O_2 content, fetal PO_2, fetal O_2 content and levels of fetal brain oxyhemoglobin decreased. The quantity of fetal brain reduced hemoglobin increased.

This investigation demonstrated that Fluosol-DA exchange of the mother delivers O_2 effectively to the fetus under the conditions of our study.

CEREBRAL METABOLISM AFTER HYPOXIC-HYPOTENSION: THE ROLE OF CALCIUM ENTRY BLOCKERS

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Hypoxic-Hypotension and Calcium Blockers

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ABSTRACT

Rats were subjected to 30 minutes of hypoxic-hypotension and then allocated to one of three treatment groups. Group I was resuscitated by restoration of FIO_2 = 30% and reinfusion of shed blood plus an equal volume of additional saline. Group II and III received in addition verapamil, .2 mg/Kg or nifedipine, 10 μg/Kg respectively. Significantly ($p<.01$) higher concentrations of creatine phosphate and ATP were present after nifedipine treatment. Using in vivo near infrared spectrophotometry, it was noted that nifedipine treated animals had significantly ($p<.01$) higher hemoglobin oxygenation.

KEY WORDS

hypoxia

hypotension

creatine phosphate

adenosine triphosphate

nifedipine

verapamil

niroscopy

INTRODUCTION

Despite improved pre-hospital care, trauma patients continue to sustain periods of cerebral hypoxia and hypoperfusion prior to definitive restoration of cerebral perfusion and oxygenation. Ames et al[1] and Rehncrona et al[2] were among the first to call attention to the fact that patchy areas of non-perfused brain persisted after a period of cerebral ischemia. Previous work from this laboratory[3] extended these observations in terms of the dynamic aspects of "no reflow" and have also focused on the post ischemic-hypoxic period in terms of high energy phosphate metabolism[4] and cytochrome oxidase function[5]. Whether the alterations noted were secondary to lack of perfusion or were the result of primary intramitochondrial damage could not be ascertained.

In view of the recent flurry of interest in calcium entry blockers and their possible effect on cerebral vasculature[6,7,8,9] this study reports an investigation of two calcium entry blockers, verapamil and nifedipine, in a clinically relevant model of hypoxic-hypotension.

MATERIALS AND METHODS

Adult, male, Sprague-Dawley rats (200-300 g) were anesthetized using sodium thiopental (50 mg/Kg) injected intraperitoneally. Two femoral artery catheters (P.E. 50-10) and one femoral vein catheter (P.E. 50) were inserted to allow anaerobic sampling of arterial pO_2, pCO_2, and pH, the withdrawal of arterial blood to produce hemorrhagic shock, and the intravenous infusion of resuscitative fluid and drugs. A tracheostomy was performed, the animals paralyzed, (tubocurarine HCl 1.5 mg/Kg) and connected to a Harvard rodent ventilator adjusted to achieve an arterial pCO_2 of 35-40 mm Hg. The FIO_2 was 30% and animals with an arterial pO_2 less than 95 mm Hg were discarded.

Experiment A - Effect of verapamil and nifedipine on cerebral high energy phosphate and lactate concentrations.

After baseline measurements were obtained, the FIO_2 was reduced to 7.5% and arterial blood withdrawn to produce a mean arterial pressure of 30 mm Hg. These conditions were maintained for 30 minutes at the end of which time end shock measurements were made. The animals were then allocated to one of three treatment groups and resuscitated as follows: Group I - restoration of FIO_2 = 30% and reinfusion of shed blood plus an equal volume of saline, Group II - restoration of FIO_2 = 30%, reinfusion of shed blood plus an equal volume of saline, and intravenous verapamil, 0.2 mg/Kg, Group III - restoration of FIO_2 = 30%, reinfusion of shed blood plus an equal volume of saline, and intravenous nifedipine, 10 μg/Kg.

At 20 and 120 minutes post-resuscitation (S + 20, S + 120) measurements were again performed. At each measurement period the dorsal cranial scalp and underlying musculature were incised and reflected and a plastic

chimney positioned on the skull. Five rats were sacrificed at each measurement period by pouring liquid nitrogen into the chimney followed by total immersion of the rat in liquid nitrogen as described by Ponten[10]. The frozen cerebral cortices were homogenized, and assayed for creatine phosphate (CP), adenosine tri-phosphate (ATP), and lactate as described by Lowry and Passoneau[11]. Arterial pH, pO_2, and pCO_2 measurements were obtained at baseline, end shock, S + 20 and S + 120.

Experiment B - Effect of verapamil and nifedipine on cerebral hemoglobin saturation, and cytochrome a,a_3 redox state as assessed by niroscopy.

After initial preparation of the animals as described above the rats were mounted in a stereotaxic apparatus. A depilatory was used to remove hair over each parieto-occipital scalp. A fiber-optic bundle for transmitting near infrared light was positioned over one parieto-occipital region and a photomultiplier tube was positioned over the ooposite parieto-occipital area for detecting transmitted light.

The principles of near infrared optical spectrophotometry (niroscopy) have been described previously[12,13]. Briefly, the niroscope provides light at three wavelengths. One is 813 nm, an absorption band for oxidized cytochrome a,a_3. Since the spectra for oxy and deoxy hemoglobin overlap that of cytochrome a,a_3, additional wavelengths at 770 nm and 905 nm allow for correction of the artifactual contribution of hemoglobin to the cytochrome a,a_3 signal while at the same time providing information regarding the concentration of oxy hemoglobin (HbO_2) and reduced hemoglobin (Hb) in the illuminated field. Summation of these two signals provides information regarding the total quantity of hemoglobin (HbT) (by inference, the blood volume) in the illuminated field. Prior to the start of the experiments, the rats were ventilated for ten minutes with 95% O_2 - 5% CO_2,

and the niroscopic readings arbitrarily called 100% oxidation. At the conclusion of the experiment, the rats are ventilated with 100% N_2, and the resulting readings arbitrarily defined as 100% reduction. Experimental data are presented as percent oxidation based on this scale.

The rats were subjected to the same hypoxic-hypotensive stress and allocated to the same treatment groups as described above under Experiment A.

Although niroscopy allows continuous non-invasive assessment, data were recorded at baseline, end shock, S + 20 and S + 120. Arterial blood for pH, pO_2, and pCO_2 were also obtained at baseline, end shock, S + 20 and S + 120. Five rats were assigned to each group.

Statistical analysis of the data in Experiments A & B was by unpaired Student's t-test.

RESULTS

There were no significant differences between Experiments A and B, or between groups at any sample time within either experiment, in terms of arterial pressure, pH, pCO_2, or pO_2. Consequently, these data are pooled and presented in Table I to illustrate the degree of severity of the hypoxic-hypotensive insult and subsequent recovery.

Experiment A

A flow diagram to aid in understanding the allocation of animals is presented in Fig. 1, and the results for cerebral cortical CP, ATP, and lactate are presented in Table II. Marked reductions in ATP and CP, and an increase in lactate concentration were noted at the end of the hypoxic-hypotensive period. Following resuscitation, Group II, verapamil, was not significantly different from Group I, control, in terms of any of the measured parameters at any sample time. This is in contrast to the significant ($p<.01$) improvement in cerebral cortical ATP and CP concentrations noted in Group III, nifedipine. Not only were the concentrations of CP and ATP significantly better than those achieved with either no treatment or verapamil, the CP concentration returned to values not significantly different from baseline.

Experiment B

The niroscopically obtained data are presented in Table III. Hypoxic-hypotension was associated with marked reduction in HbO_2, with a reciprocal increase in Hb, and a reduction in HbT. There was a concomitant reduced cytochrome $\underline{a},\underline{a}_3$ redox state. There were no significant differences after resuscitation between Group I, control, and Group II, verapamil in terms of the cytochrome $\underline{a},\underline{a}_3$ redox state, HbO_2, Hb or HbT.

A statistically significant increase in HbO_2 ($p<.01$) was noted in the nifedipine treated rats with a reciprocal decrease in Hb, most marked at S + 20. This was not associated with a more oxidized cytochrome $\underline{a},\underline{a}_3$ or an increase in HbT.

DISCUSSION

Calcium ion shifts have been linked to a wide variety of abnormalities in cellular metabolism, intracellular release of free fatty acids, production of oxidative free radicals, and the no reflow phenomenon in the brain. The gradient for Ca^{++} from outside to inside the cell is 10,000:1[14]. Maintenance of this gradient is believed to be energy dependent and influx of Ca^{++} into the cell is via two routes, a "fast channel" and a "slow channel". The reader is referred to reviews by White et al[6] and Merin[15] but briefly an outer and inner gate have been postulated for each channel with functionally different characteristics. The outer gates respond to voltage changes generated by an electrical stimulus with the slow channel outer gate being blocked by nifedipine. The inner gates appear to be more dependent on the phosphorylation state of the membrane protein, and are affected by verapamil. It was on the basis of these different pharmacologic modes of action, as well as the preferential cerebrovascular action of nifedipine type drugs[16] that led us to evaluate both nifedipine and verapamil in this experimental model of hypoxia and hypotension.

Despite the potential benefit of verapamil blocking calcium influx during periods of decreased oxidative phosphorylation, there appeared to be no beneficial effect in this model in terms of the parameters measured. This was in contrast to the response following the administration of nifedipine. Although cardiac output was not measured in these rats, in view of the lack of difference in mean arterial pressure in the three groups it seems reasonable to suppose that the cardiac outputs were not markedly different, and thus, the beneficial effect of nifedipine is more apt to be on an intracerebral basis rather than the result of a more generalized improvement in blood flow from improved cardiac function. Considering the potential sites of action for

nifedipine (cerebrovascular vs. neuronal) the increased HbO_2 favors a direct action of nifedipine on the smooth muscle of the cerebral vasculature. Since the arterial pO_2 and acid base status of the animals were similar, increases in brain HbO_2 in Group III are probably not due to differences in arterial saturation or vascular dilatation secondary to increases in hydrogen ion concentration. The fact that the total brain blood volume did not increase as judged by the lack of difference between groups in HbT is not inconsistent with the nifedipine effect being largely a vascular phenomenon. The bulk of the blood in the illuminated field resides in the large venous sinuses, thus a small increase in blood volume on the arterial side might well be missed. Secondly, assuming no reflow, the non re-perfused capillaries are filled with stagnant blood. If nifedipine's mode of action were to enhance re-perfusion, the quantity of hemoglobin in the illuminated field would not necessarily be increased, but rather the increased number of perfused capillaries would produce a shift away from Hb toward HbO_2 as we observed, with subsequent improvement in brain ATP and CP concentration.

The foregoing should not be construed to mean that the only site of action for nifedipine is vascular. It is quite possible that in addition to the vascular effect we have observed, nifedipine is preventing an influx of Ca++ into the cytosol. Lehninger[17] has called attention to the fact that exposure of liver mitochondria to calcium and substrate results in greatly increased oxygen consumption accompanied by pumping of protons out of the mitochondria with the mitochondrial uptake of calcium. This energy of oxidation is directly used by the mitochondria to take up calcium without the intermediate production of ATP as opposed to the state when normal cytosolic concentrations of calcium allow the pumping out of H^+ and then its return back across the mitochondrial

membrane along the chemiosmotic gradient[18] with the production of ATP. Such a state would produce higher concentrations of ATP and CP consistent with the observations in this study. If, however, the observed increases in ATP and CP were explainable to any great extent on an increased brain cytosol calcium concentration being prevented by nifedipine, it would be difficult to explain the apparent lack of effect of verapamil.

CONCLUSIONS

We conclude, therefore, on the basis of these preliminary studies, (a) improved high energy phosphate concentrations, and increased concentrations of brain HbO_2 result from nifedipine treatment, (b) the apparent lack of effect of verapamil in the same model indicates the preferential effect of nifedipine is probably on the smooth muscle of the cerebral vasculature rather than a direct effect within the neuron, and (c) since we observed the effect when nifedipine was administered post hypoxia and hypotension, continued investigation leading to an eventual clinical trial appears warranted.

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TABLE I

Experiment A & B

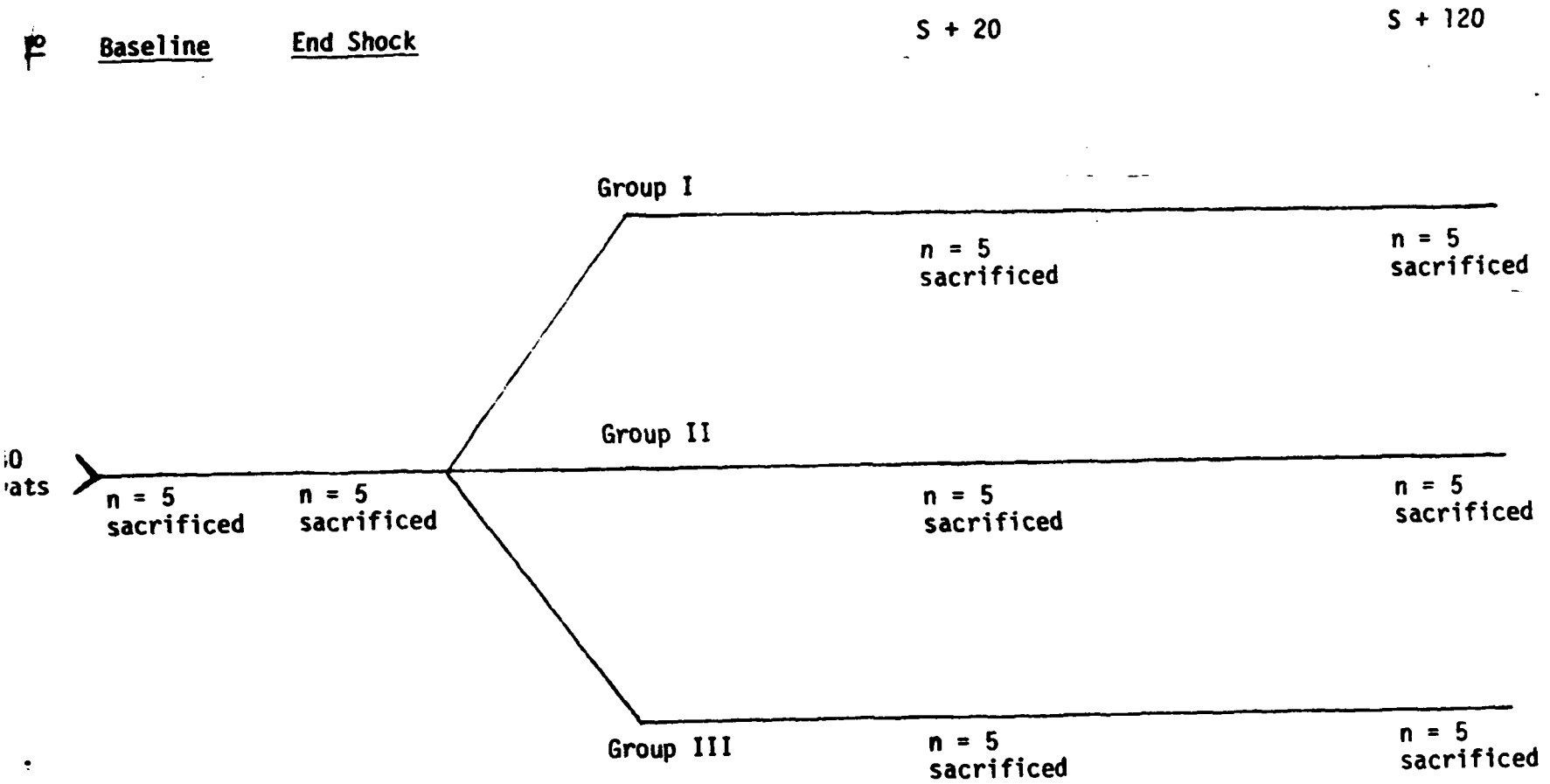
		Baseline	End Shock	S + 20	S + 120
MAP	$\bar{x}$	121.0	30	73.0	96.0
	s.e.	6.56	0	4.01	3.52
	n	30	30	30	30
pH	$\bar{x}$	7.39	7.16	7.13	7.24
	s.e.	.01	.15	.03	.02
	n	30	30	30	30
pCO_2	$\bar{x}$	36.4	30.1	33.2	36.9
	s.e.	4.5	2.2	2.23	.79
	n	30	30	30	30
pO_2	$\bar{x}$	117.0	63.0	110.0	104.0
	s.e.	2.62	5.5	10.04	5.14
	n	30	30	30	30

LEGEND - TABLE I

Mean ($\bar{x}$), standard error (s.e.) and number of animals (n) for all groups. Experiments A & B for mean arterial pressure (MAP), pH, pCO_2, and pO_2.

FIGURE 1

Experiment A



LEGEND - FIGURE 1

Flow diagram illustrating allocation of rats to treatment groups and time and number of rats sacrificed in Experiment A.

TABLE II

Experiment A

		Baseline	End Shock
CP	$\bar{x}$	3.04	1.15
	s.e.	.25	.45
	n	5	5
ATP	$\bar{x}$	2.73	1.75
	s.e.	.04	.20
	n	5	5
lactate	$\bar{x}$	.78	9.22
	s.e.	.09	1.19
	n	5	5

		Group I		Group II		Group III	
		S + 20	S + 120	S + 20	S + 120	S + 20	S + 120
CP	$\bar{x}$	1.70	2.56	2.27	2.44	2.90	3.33
	s.e.	.60	.19	.16	.14	.30	.33
	n	5	5	5	5	5	5
ATP	$\bar{x}$	2.09	1.82	1.91	2.05	2.39	2.45
	s.e.	.12	.12	.11	.14	.06	.05
	n	5	5	5	5	5	5
lactate	$\bar{x}$	3.74	.70	5.08	.91	3.35	2.20
	s.e.	1.49	.11	1.04	.29	1.29	1.39
	n	5	5	5	5	5	5

LEGEND - TABLE II

Results of Experiment A. Data for mean ($\bar{x}$), standard error (s.e.) and number of observations (n) are presented in μ moles/g of wet cortex. Rats were sacrificed to describe baseline (n = 5) and end shock (n = 5) values establishing the severity of the hypoxic-hypotensive period and the concentrations immediately prior to allocation to treatment group (see Fig. 1).

TABLE III

Experiment B

		Baseline	End Shock
Hb	$\bar{x}$	17.3	70.0
	s.e.	1.13	4.02
	n	15	15
HbO_2	$\bar{x}$	84.7	7.03
	s.e.	.86	2.36
	n	15	15
HbT	$\bar{x}$	100.0	75.1
	s.e.	-	±4.31
	n	15	15
Cyt. $\underline{a},\underline{a}_3$	$\bar{x}$	90.8	33.65
	s.e.	1.05	2.89
	n	15	15

		Group I		Group II		Group III	
		S + 20	S + 120	S + 20	S + 120	S + 20	S + 120
Hb	$\bar{x}$	20.2	20.1	17.3	24.2	9.9	15.1
	s.e.	1.15	2.21	2.50	2.18	3.6	2.70
	n	5	5	5	5	5	5
HbO_2	$\bar{x}$	76.7	74.5	77.3	74.2	85.2	78.0
	s.e.	5.35	4.12	3.50	4.31	3.7	4.70
	n	5	5	5	5	5	5
HbT	$\bar{x}$	101.7	95.4	93.2	85.1	93.9	98.1
	s.e.	3.51	2.05	4.22	4.48	2.74	2.27
	n	5	5	5	5	5	5
Cyt. $\underline{a},\underline{a}_3$	$\bar{x}$	85.6	91.6	80.7	71.5	85.2	80.5
	s.e.	5.15	7.40	3.48	3.60	3.72	3.96
	n	5	5	5	5	5	5

LEGEND - TABLE III

Mean ($\bar{x}$), standard error (s.e.), and number of observations (n) for reduced hemoglobin (Hb), oxidized hemoglobin (HbO_2), total hemoglobin (HbT), and cytochrome $\underline{a},\underline{a}_3$ redox state (Cyt. $\underline{a},\underline{a}_3$). HbT is presented as percent change from baseline, all other data as percent oxidation. Baseline and end shock data were collected from all 15 animals prior to allocation to each group (n = 5).